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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/938,200	08/23/2001	Carmel M. Lynch	226272001702	2669

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EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 09/10/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/938,200	Applicant(s) LYNCH ET AL.	
	Examiner Michael Wilson	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1632.

Claims 1-16 are under consideration in the instant application.

The IDS filed 3-5-02, paper number 3, has been entered. Documents 14-16, 18, 22, 27, 28, 30, 31, 34, 37, 39, 41, 51-53, 61, 74, 75, 83, 84, 94, 96, 110-112, 116, 121 and 122 have not been considered because they are tables of contents. Documents 24 and 117 have not been considered because they have not been provided. Documents 1-13, 17, 19-21, 23, 25, 26, 29, 32, 33, 35, 36, 38, 40, 42-50, 54-60, 62-73, 76-82, 85-93, 95, 97-109, 113-115, 118-120 and 123 have been considered.

Specification

The first line of the specification needs updated to reflect the fact that the parent case has been abandoned.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising administering an AAV vector comprising a nucleotide sequence encoding a marker protein operatively linked to a promoter into an artery following balloon catheter injury such that expression of the marker protein occurs in adventitial, microvascular endothelial cells, does not reasonably provide enablement for merely introducing an AAV vector into a blood vessel, introducing an AAV vector comprising a therapeutic gene, treating an individual by transducing a cell with an AAV vector encoding a therapeutic gene, introducing an AAV vector into a microvessel or into the adventitia of an artery without using a balloon catheter, or transducing microvascular cells without using a balloon catheter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 is directed toward transducing cells of a blood vessel *in vivo* by introducing an AAV vector into a blood vessel. Claim 14 requires the AAV vector is introduced into the adventitia of an artery. Claim 15 is directed toward a cell produced by introducing an AAV vector. None of the claims require expression of a protein encoded by the AAV vector. Mere introduction of an AAV into a blood vessel or cell does not have a use that is enabled in the specification or the art at the time of filing. What is required is expression of the protein. As such the claims should clearly set forth that introducing AAV results in expression of a protein encoded by the AAV. It is noted that for protein expression to occur, the AAV vector must

comprise a nucleic acid sequence encoding a protein operably linked to a promoter. The promoter is essential to obtain protein expression because it cannot occur otherwise.

Claim 1 is directed toward transducing cells of a blood vessel *in vivo* by introducing an AAV vector into a blood vessel. Dependent claims require the blood vessel is a microvessel (claims 5-7), the cell is a microvascular cell (claims 11-13) or introducing the vector into the adventitia (claim 14). Claim 15 is directed toward a transduced microvascular cell. The specification teaches injecting AAV into blood vessels following balloon catheter injury resulted in expression in microvessels, microvascular cells or the adventitia (pg 31, Example 4; pg 32, line 25). The specification teaches injecting AAV into blood vessels without using balloon catheter injury did not result in expression in microvessels, microvascular cells or the adventitia (pg 32, line 27, "control artery"; pg 29, Example 3; pg 31, line 16). Lynch (1997, Circulation Res., Vol. 80, pg 497-505) confirmed that expression was "found only in the adventitia of one of the two denuded common carotid arteries (pg 501, col. 2, 8 lines from the bottom). The art at the time of filing did not teach obtaining expression in microvessels, microvascular cells or the adventitia by injecting AAV into a blood vessel without a balloon catheter. Given the teachings in the art taken with the guidance in the specification it would require one of skill undue experimentation to determine how to obtain delivery or expression in microvessels, microvascular cells or the adventitia without a balloon catheter as broadly encompassed by the claims.

Claim 4 requires the AAV vector comprises a therapeutic gene. Claim 16 is directed toward treating an individual for disease using an AAV vector comprising a therapeutic gene. Claims 4 and 16 do not require obtaining any therapeutic effect. "Treating an individual for a disease condition" in claim 16 is an intended use and does not bear patentable weight because it may not occur. The only purpose of administering AAV vectors comprising therapeutic genes is for obtaining a therapeutic effect (pg 2, line 13; pg 7, line 21). Mere introduction of an AAV comprising a therapeutic gene into a blood vessel or cell as claimed does not have a use that is enabled in the specification or the art at the time of filing.

Furthermore, the specification does not enable one of skill to use the claimed invention to obtain a therapeutic effect. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews

new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus, it was unpredictable what combination of elements were required to obtain a therapeutic effect using gene therapy by introducing AAV encoding a therapeutic gene into the blood vessel.

The specification teaches administering AAV vectors encoding marker proteins to the adventitial microvessels of an artery in a cholesterol fed monkey model (Examples 3-7; pages 29-37). The specification contemplates delivering therapeutic genes to treat atherosclerosis (page 21, line 16). The specification does not teach the amount of protein expression required to obtain a therapeutic effect, the target cells of the blood vessel required to obtain the desired effect or the effect of expression in cells of microvessels. The specification does not teach obtaining a therapeutic effect by introducing AAV into a blood vessel. Nor did the art at the time of filing

teach administering AAV into a blood vessel caused a therapeutic effect. Given the state of the art at the time of filing taken with the teachings in the specification and the lack of correlation between marker proteins and therapeutic proteins, the lack of guidance regarding the parameters required to target the desired tissue and obtain a therapeutic effect, and the breadth of the claims, it would have required one of skill in the art at the time the invention was made undue experimentation to determine the parameters required to obtain a therapeutic effect by introducing an AAV encoding a therapeutic protein into a blood vessel.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-14 are indefinite because the preamble and the body of the claims are not commensurate in scope. The preamble is directed toward "transducing a cells in a blood vessel" but the body of the claim merely requires introducing AAV into a blood vessel. The body of the claim does not require transducing any cells in the blood vessel, thus making the claims unclear.

Claim 1 is indefinite because it is unclear if the blood vessel in the body of the claim is the same blood vessel in which the cell is transduced.

Claims 5-7 are indefinite because it is unclear if "said blood vessel" refers to the blood vessel in the preamble or the blood vessel in the body of the claim. As such, it cannot be determined whether claims 5-7 further limit the blood vessel into which the AAV is introduced or the blood vessel in which the cell is transduced.

Claim 16 is indefinite because the preamble and the body of the claims are not commensurate in scope. The preamble is directed toward "treating an individual for a disease" but the body of the claim merely requires introducing AAV into a blood vessel. The body of the claim does not require treating an individual or treating disease, thus making the claim unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

3. Claims 1-16 are rejected under 35 U.S.C. 102(e) as being anticipated by Kaplitt (US Patent 6,162,796, Dec. 19, 2000).

Kaplitt administered an AAV vector encoding lacZ into the mid-circumflex coronary artery using a catheter and obtained expression in the heart (col 14, lines 33-51, Fig. 1-3, col. 5, line 61 through col. 6, line 1). Kaplitt delivered an AAV vector encoding various proteins and

expressed the protein in various "target cells," including vascular endothelial cell and human cells (see claims 1, 9, 23 and 24). Thus, Kaplitt anticipates the claims.

The phrase "transducing a cell in a blood vessel" in the preamble of claim 1 is an intended use and does not bear patentable weight because it may not occur. Claims 5-13 are included because they further limit the preamble.

Claim 10 is also included because the target cells of Kaplitt are inherently proliferating because all cells regenerate.

Claim 15 is also included because the transduced vascular endothelial cell of Kaplitt (claim 9) has the same structure as a "microvascular" endothelial cell transduced with AAV.

Claim 16 is included because "treating an individual for a disease condition" is an intended use and does not bear patentable weight in considering the art because it may not occur.

4. Claims 1-13, 15 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Podsakoff (US Patent 5,858,351, Jan. 12, 1999).

Podsakoff taught delivering a recombinant AAV vector encoding EPO operatively linked to a promoter into the tail vein of mice and obtaining detectable expression of EPO in the serum (col. 20, lines 1-20; col. 22, lines 8-19; Fig. 7). The phrase "transducing a cell in a blood vessel" in the preamble of claim 1 is an intended use and does not bear patentable weight because it may not occur. Claims 5-13 are included because they further limit the preamble. Claim 10 is also included because the cells that express EPO are inherently proliferating. Claim 15 is included because the cells transduced with AAV in the method of Podsakoff have the same structure as a

"microvascular cell" transduced with AAV. Claim 16 is included because "treating an individual for a disease condition" is an intended use and does not bear patentable weight in considering the art because it may not occur.

Podsakoff also taught transducing myocytes of the heart by injecting AAV into the left ventricular apex of the heart (col. 22, lines 41-52). Injecting AAV into the left ventricular apex of the heart is equivalent to introducing AAV into a blood vessel as claimed because the heart is a vessel containing blood. The myocytes expressing β-gal are inherently proliferating.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branellec (US Patent 5,851,521, Dec. 22, 1998), as supported by Nabel (5,328,470, July 12, 1994).

Branellec taught delivering an adenoviral vector encoding GAX or lacZ into rat arteries following balloon catheter injury and obtaining expression in the blood vessel (col. 16, lines 45-65; col. 22, lines 26-39; col. 22, Table 3, "treated artery"). Branellec did not expressly teach

introducing AAV into blood vessels. However, Branellec taught the invention could be performed using AAV vectors (col. 6, lines 56; col. 7, line 56 through col. 8, line 29).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver a vector encoding GAX or lacZ into rat arteries following balloon catheter injury and obtain expression in the blood vessel as taught by Branellec wherein the vector was AAV as taught by Branellec. One of ordinary skill in the art at the time the invention was made would have been motivated to use AAV instead of adenovirus because Branellec suggested using AAV in the method (col. 6, lines 56; col. 7, lines 56 through col. 8, line 29).

Balloon catheter injury as taught by Branellec inherently results in proliferation of cells in the injured wall because the response to the injury is to regenerate the cells of the blood vessel which requires proliferation of the remaining cells. Administering AAV after balloon catheter injury as taught by Branellec inherently results in transduction of microvascular cells of the adventitia (pg 1, lines 20-27; pg 10, lines 3-16) because balloon catheter injury is the method used by applicants to obtain transduction of microvascular cells of the adventitia (page 36, lines 6-13). Nabel taught administering a viral vector to a blood vessel following balloon catheter injury results in delivery and expression in the adventitia (para. bridging pg 249-250). Therefore, Nabel supports the inherency of transducing microvascular cells of the adventitia after balloon catheter injury.

Reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

6. Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branellec (US Patent 5,851,521, Dec. 22, 1998) in view of Kaplitt (US Patent 6,162,796, Dec. 19, 2000), as supported by Nabel (5,328,470, July 12, 1994).

Branellec taught delivering an adenoviral vector into an artery following balloon catheter injury and obtaining expression in the artery (col. 16, lines 45-65; col. 22, lines 26-39; col. 22, Table 3, "treated artery"). Branellec did not expressly teach using an AAV vector in the method.

However, Kaplitt taught administering an AAV vector into an artery using a catheter and obtaining expression in the heart (col 14, lines 33-51, Fig. 1-3, col. 5, line 61 through col. 6, line 1). Kaplitt also taught delivering an AAV vector encoding various proteins, some of which are "therapeutic," to a blood vessel and expressing the protein in various "target cells," including vascular endothelial cell and human cells (see claims 1, 9, 23 and 24).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer a viral vector to a blood vessel following balloon catheter injury as taught by Branellec using an AAV vector as taught by Kaplitt. One of ordinary skill in the art at the time the invention was made would have been motivated to replace the adenoviral vector of Branellec with the AAV vector of Kaplitt because Branellec taught the method could also be performed using AAV (col. 6, lines 56; col. 7, line 56 through col. 8, line 29).

Balloon catheter injury as taught by Branellec inherently results in proliferation of cells in the injured wall because the response to the injury is to regenerate the cells of the blood vessel which requires proliferation of the remaining cells. Administering AAV after balloon catheter injury as taught by the combined teachings of Branellec and Kaplitt inherently results in transduction of microvascular cells of the adventitia (pg 1, lines 20-27; pg 10, lines 3-16) because balloon catheter injury is the method used by applicants to obtain transduction of microvascular cells of the adventitia (page 36, lines 6-13). Nabel taught administering a viral vector to a blood vessel following balloon catheter injury results in delivery and expression in the adventitia (para. bridging pg 249-250). Therefore, Nabel supports the inherency of transducing microvascular cells of the adventitia after balloon catheter injury.

Reliance upon inherency is not improper even though rejection is based on Section 103 instead of Section 102. In re Skoner, et al. 186 USPQ 80 (CCPA).

Thus, Applicants' claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

7. Claim 11 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 7. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP §

706.03(k). If claim 7 is limiting the blood vessel in which the cell is transduced, transducing a microvascular cell is equivalent to transducing a cell of a microvessel.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

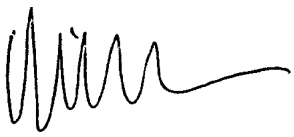
Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson



MICHAEL C. WILSON
PATENT EXAMINER